

### REMARKS

Applicants thank the Examiner for the very thorough consideration given the present application. Claims 2-12, 15 and 16 are currently pending in this application. None of the claims have been amended. Accordingly, no new matter has been added.

In view of the remarks herein, Applicants respectfully request that the Examiner withdraw all outstanding rejections and allow the currently pending claims.

#### Issues Under 35 U.S.C. § 103

Claims 2-12, 15 and 16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 5,811,446 (hereinafter "Thomas"), in view of U.S. Patent 5,994,372 (hereinafter "Yaksh") and U.S. Patent 5,116,868 (hereinafter "Chen"). Applicants respectfully traverse.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the Examiner must make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). "[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ 2d 1385 (U.S. 2007). There must be a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *Id.* The Supreme Court of the United States has recently held that the "teaching, suggestion, motivation test" is a valid test for obviousness, albeit one which cannot be too rigidly applied. *Id.*

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

The present invention is directed, inter alia, to a method of treating tear abnormalities. One of the novel features of the present invention is that 3-hydroxybutyric acid or salts thereof can be effectively employed in the treatment of tear abnormalities of patients having tear abnormalities (see, e.g., claim 12).

Thomas teaches that histidine or a therapeutic composition containing histidine are effective in the treatment of posterior segment diseases, such as glaucoma or macular degeneration (see column 3, lines 40-50 and column 6, line 65 to column 7, line 10 of Thomas).

Thomas also teaches that ocular inflammations arising from accidental contact of the eye surface with cosmetics or physical trauma to the eye surface from a mascara or liquid eyeliner brush, etc. are treated by administering histidine after their occurrence (see column 7, lines 11-25). Thomas further teaches that histidine is formulated into cosmetics in advance (see column 7, lines 25-30). In this case, Thomas recommends that eye cosmetic materials having cell regeneration activity should be compounded into the cosmetics together with histidine (see column 7, lines 30-32). Thomas teaches that  $\alpha$ - or  $\beta$ -hydroxyacid,  $\alpha$ -hydroxybutyric acid and  $\alpha$ -hydroxyisobutyric acid are examples of eye cosmetic materials having cell regeneration activity (see column 7, lines 34-40).

As obvious from the above, Thomas teaches that histidine is effective in the treatment of posterior segment diseases and that  $\alpha$ - or  $\beta$ -hydroxyacid,  $\alpha$ -hydroxybutyric acid and  $\alpha$ -hydroxyisobutyric acid have cell regeneration activity. However, Thomas fails to teach that  $\alpha$ -

or  $\beta$ -hydroxyacid or the like are effective in the treatment of posterior segment diseases. Thomas merely teaches that  $\alpha$ - or  $\beta$ -hydroxyacid or the like are contained in cosmetics. Thomas does not in any way teach or suggest a method using a therapeutic composition containing  $\alpha$ - or  $\beta$ -hydroxyacid as claimed.

Consequently, if posterior segment diseases manifest some form of tear abnormality, it does not follow from the teachings of Thomas that  $\alpha$ -hydroxybutyric acid or salts thereof are effective in the treatment of such tear abnormality.

Yaksh and Chen fail to cure the deficiencies of Thomas. Yaksh discloses a drug for treating hyperalgesia in the peripheral nervous system. The nerve terminals not only accept pain, but also secrete a chemical substance known as "substance P" by axon reflex. This chemical substance acts on a mast cell to release histamine, produces another algestic substance and causes vascular dilation. When a tissue is damaged, various algestic substances, such as prostaglandin, potassium and bradykinin, are secreted. In this state where the nerve terminal is continuously immersed in algestic substances, sensitivity to pain of a nerve significantly rises, thereby developing (peripheral) hyperalgesia. However, Applicants submit that the mechanism by which (peripheral) hyperalgesia develops involves algestic substances, which differs completely from the mechanisms involved in dry eye, which are targeted by the present invention. As such, the skilled artisan, wanting to treat the diseases described in present claim 12, would not look to an anti-hyperalgesia compound, such as that described by Yaksh.

Chen discloses an ophthalmic irrigation solution containing  $\beta$ -hydroxybutyric acid. However, Chen does not teach or suggest the use of the solution as a treating drug (see, e.g., col. 6, lines 7-8, wherein it is explicitly disclosed that the ophthalmic irrigation solution is not

intended for use as a therapeutic agent). Ophthalmic irrigation solutions are used to clean the inside of the eye and to prevent drying on the surface of the eye during ophthalmic surgery. As such, one skilled in the art would not think of using the ophthalmic irrigation solution of Chen for the treatment of the eye diseases listed in claim 12 of the present application.

Evidently, the cited references, alone or in combination, fail to teach or suggest every limitation of the instant invention. Moreover, Applicants respectfully submit that there is no rational underpinning to support the legal conclusion of obviousness, since the skilled artisan would not have been motivated to combine and modify the references as proposed.

Reconsideration and withdrawal of this rejection are respectfully requested.

### Conclusion

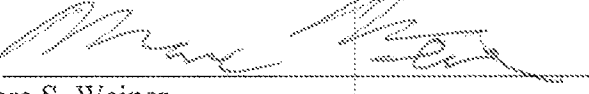
All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and objections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Vanessa Perez-Ramos, Reg. No. 61,158, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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